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Effect of Triethyltin on Autonomic and Behavioral Thermoregulation of Mice[1]

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Effect of Triethyltin on Autonomic and Behavioral Thermoregulation of Mice. GORDON, C. J., LONG, M. D., AND DYER, R. S. (1984). *Toxicol. Appl. Pharmacol.* 73, 543–550. The organotin compound, triethyltin (TET), produces toxic effects in a variety of physiological systems. Thermoregulatory control appears to be especially susceptible to TET toxicity, since TET administration has been shown to cause a pronounced hypothermia in rats. To further elucidate effects of TET on thermoregulation, we measured metabolic rate, evaporative water loss (EWL), body temperature, and preferred ambient temperature (T_a) of mice treated intraperitoneally with TET (bromide salt). At a T_a of 23 to 24°C, TET (6 and 8 mg/kg) inhibited metabolic rate by 23 and 66%, respectively. TET resulted in hypothermia at T_a's of 20 and 30°C but not 35°C. TET had little effect on EWL. Mice given TET at doses of 4, 6, and 8 mg/kg selected a cooler T_a (ca. 25°C) compared to controls (ca. 29°C). Thus, the mice selected a T_a associated with a hypothermic body temperature. At a relatively cool T_a, mice treated with TET had a reduced rate of heat production and, consequently, were hypothermic. At a relatively warm T_a, TET had no effect on heat production and did not increase active heat dissipation (i.e., EWL), thus the mice remained normothermic. The behavioral data indicate that TET evokes a type of regulated hypothermia in mice.

Triethyltin (TET), an extremely toxic organotin compound (Kimbrough, 1976), has been shown to be a potent inhibitor of cellular metabolism (Brody and Moore, 1962; Aldridge and Rose, 1969; Cremer, 1970). A variety of anatomical and functional neurotoxic effects, such as demyelination (Blaker *et al.*, 1981), ataxia (Gerren *et al.*, 1976), and increased latency for a visual-evoked response (Dyer and Howell, 1982), have been demonstrated in animals injected with TET.

Intraperitoneal TET administration to the rat at an ambient temperature of 22°C results in a prolonged hypothermic state than can last up to 24 hr (Dyer and Howell, 1982). Intravenous administration of TET to the rat also causes hypothermia, whereas, intracerebroventricular injection causes a biphasic temperature response, hypothermia followed by hyperthermia (Leow *et al.*, 1980). TET-induced hypothermia can be partially attenuated by raising ambient temperature from 22 to 30°C (Dyer and Howell, 1982). Interestingly, one neurotoxic effect of TET, delay in the visual evoked response, is more pronounced at a higher ambient temperature (Dyer and Howell, 1982). Thus, the observed hypothermia following TET may be independent of the neurotoxicity. In a related study, Cremer (1970) found that TET effects on glucose metabolism in the brain were not directly attributable to hypothermia.

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Toxic as well as other agents which affect thermoregulation may induce either a forced or regulated change in body temperature (Gordon, 1983). For example, TET-induced reduction in body temperature could be a forced hypothermia meaning that heat gain and/or heat conservation is inhibited with no change in set-point. That is, body temperature is below its regulated or preferred level and the animal's response is to select a warm environment and/or increase heat production (if possible) in an attempt to raise body temperature back to normal. If the hypothermia is regulated, then there is a decrease in set-point whereby the animal lowers heat production, increases heat loss, and behaviorally selects a cooler environment which leads to a controlled decrease in body temperature.

Discerning forced from regulated changes in body temperature is important to toxic studies. The ambient conditions may be crucial depending on whether a toxic-induced temperature change is forced or regulated. For example, during forced hypothermia, a warm ambient temperature is preferable to the animal since there is a physiological and behavioral drive to elevate body temperature back to normal. However, a warm ambient temperature becomes stressful in regulated hypothermia since the response of the animal is to dissipate heat and maintain body temperature at a lower than normal level. The data of Dyer and Howell (1982) suggest that such mechanisms may occur since it was shown that preventing the TET-induced hypothermia by raising ambient temperature accentuated its neurotoxic effects.

This study was designed to measure body temperature, metabolic rate, evaporative heat loss, and behavioral temperature preference of mice treated intraperitoneally with TET.

METHODS

Animals used in this study were young adult, male mice of the BALB/c strain obtained from Jackson Laboratories (Bar Harbor, Maine). The animals were maintained in groups of five in cages lined with wood chip bedding at 22°C under a 12:12-hr light:dark photoperiod with *ad libitum* access to feed (Lab-Blox, Wayne Pet Food) and water.

Metabolic rate, evaporative heat loss, and body temperature. Metabolic rate was measured in single mice maintained in a temperature controlled, stainless-steel environmental chamber which had a volume of 1950 ml. Single mice were placed in a wire cage which was inserted into the environmental chamber. Dry air was pulled through the chamber at a flow rate of approximately 2500 ml/min. A small fraction of the effluent air from the environmental chamber was pulled through a dew point hygrometer (General Eastern, Model 1200 APS) to measure the dew point temperature of the air. The same air sample was dried over calcium anhydrite and then passed through an oxygen analyzer (Applied Electrochemistry) to measure the percentage oxygen. Evaporative water loss was calculated from the dew point temperature by previously published methods (Wood, 1970; Gordon, 1982). Consumed oxygen was calculated from the change in percentage oxygen of the air passing through the chamber multiplied by the flow rate. Metabolic rate (watts) was calculated assuming that 1.0 ml of consumed oxygen was equivalent to 20.1 joules (Kleiber, 1975). A layer of mineral oil placed beneath the wire-mesh cage prevented the urine and fecal moisture from interfering in the measurement of dew point temperature.

An initial experiment (N = 19) was run to assess the effects of acute TET administration on metabolic rate. The average body weight of the mice in this experiment was 25.4 ± 1.8 (SD) g. The experiments were run at an ambient temperature (T_a) of 23 to 24°C. Single mice were injected ip with the saline vehicle or TET (bromide salt) at doses of 2, 4, 6, and 8 mg/kg in a volume of 0.3 ml/100 g body weight. Naive mice were injected and placed in the environmental chamber. Four to five mice were used in each dose group. Oxygen consumption data between 30 to 60 min post-TET injection were averaged to one value and converted to metabolic rate (watts per kilogram). Sixty minutes after injection, the animal was removed from the environmental chamber, marked, and returned to the animal quarters.

In a second experiment (N = 46) metabolic rate, evaporative water loss (EWL), and body temperature were measured at T_a's of 20, 30, and 35°C. In these experiments TET doses of 0, 6, and 8 mg/kg were administered ip. The average body weight was 24.8 ± 1.5 g. The animals were treated as described above. Four to five mice were used in each treatment group. Immediately after TET injection, the mice were placed in the environmental chamber maintained at either 20, 30, or 35°C. Sixty minutes after being placed in the chamber the mouse was removed and a thermistor temperature probe (Yellow Spring Instruments) was inserted 2.5 cm past the anal sphincter. The probe was maintained for approximately 10 sec while the measurement of colonic temperature stabilized. Similar to the earlier experiment, metabolic rate and evaporative water loss were calculated from av-

erages of percentage oxygen and dew point temperature, respectively, taken over 30 to 60 min post-TET injection.

Behavioral temperature regulation. Preferred ambient temperature of mice ($N = 45$) was measured by using a longitudinal temperature gradient–shuttlebox system which has been described (Gordon *et al.*, 1983). Briefly, the system consists of a rectangularly shaped metal tube positioned between hot and cold water baths which generate a temperature gradient along the length of the metal tube. A Plexiglas shuttlebox is placed inside the metal tube and the position of the mouse inside the shuttlebox is recorded continuously by a phototransitor-based detection system.

Temperatures in the shuttlebox ranged from 19°C at the cool end to 36°C at the warm end. The shuttlebox had a length of 76 cm. Single mice were injected ip with TET at doses of 0, 2, 4, 6, and 8 mg/kg and placed in the gradient on the coolest end. The average body weight of the mice was 22.3 ± 1.5 g. Nine naive mice were used for each treatment group. The position of the mouse in the shuttlebox was monitored for 60 min. Average preferred T_a in the temperature gradient during 0 to 20, 20 to 40, and 40 to 60 min post-TET injection was calculated.

Statistical analysis. For each of the three experiments, α was maintained at 0.05 by the following procedures. The data collected on dose of TET and metabolic rate were analyzed with a univariate ANOVA, followed by Bonferroni-corrected T tests for individual comparisons. The experiment testing the effect of TET on metabolism, body temperature, and evaporative water loss at different ambient temperatures was statistically analyzed by a Multivariate two factor (dose · ambient temp) analysis of variance (MANOVA), Hotelling–Lawley procedure, with body weight of the animal as a covariate. The MANOVA was followed by univariate Bonferroni-corrected ANOVAs, which were followed in turn by Bonferroni-corrected T tests. The behavioral temperature selection experiment was analyzed with a univariate two factor repeated measures design (dose · time). Between group comparisons were made with Tukey's tests (Muller *et al.*, 1983).

RESULTS

Examples of the time course of metabolic rate of mice injected ip with saline or TET at 8 mg/kg are shown in Fig. 1. Immediately after TET injection there was an inhibition of metabolic rate lasting for the 60-min experimental period. Overall, metabolic rate was reduced significantly by TET ($F(4,18) = 22.41$, $p < 0.0001$). The hypometabolic effect of TET was due entirely to the reduction by 23 and 66% ($p < 0.001$) at doses of 6 and 8 mg/kg, respectively (Fig. 2). TET doses of 2 and 4 mg/kg had no effect on metabolic rate.

We used two dose levels of TET that inhibit metabolism in the BALB/c mouse (6 and 8 mg/kg) to test the interaction between dose and ambient temperature on metabolism,

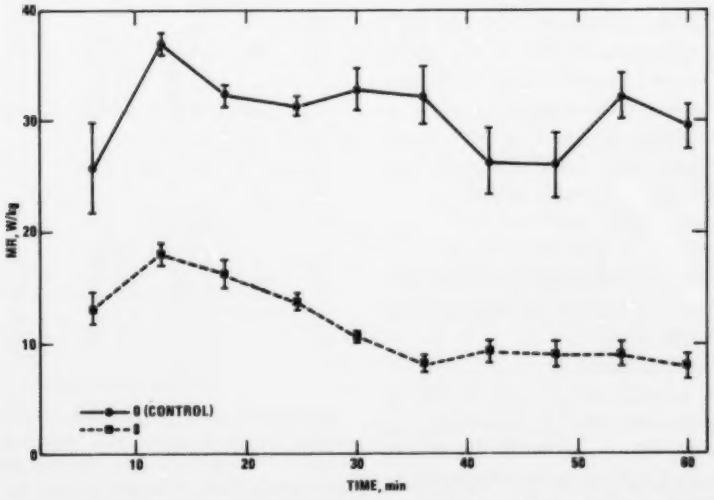

FIG. 1. Mean ± standard error of metabolic rate of mice treated with 0 and 8 mg/kg triethyltin (TET) at an ambient temperature (T_a) of 23 to 24°C. $N = 4$ to 5 for each treatment. W/kg = watts/kg.

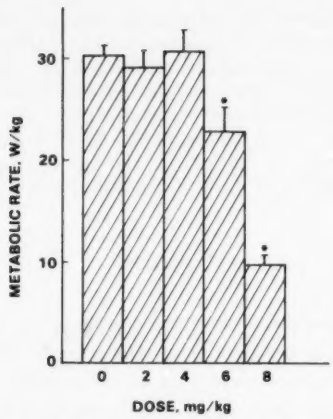

FIG. 2. Overall effect of dose of TET on metabolic rate of mice treated at a T_a of 23 to 24°C. $N = 4$ to 5 for each dosage. Vertical bars represent one standard error from mean. *Different from control, $p < 0.05$.

body temperature, and evaporative water loss. The MANOVAs indicated significant overall dose ($F(10,54) = 10.9$, $p < 0.0001$) and dose–ambient temperature interactions on these dependent variables ($F(20,106) = 7.70$, $p < 0.0001$). ANOVAs indicated that metabolic rate and colonic temperature contributed to these interactions (F's(4,31) > 6.4, p's < 0.0007). Figure 3A illustrates that at a T_a of 20°C metabolic rate was inhibited by TET in a similar manner as shown in the initial experiments run at 23 to 24°C (Fig. 2). Raising T_a to 30°C reduced the inhibitory effect of TET on metabolism, and at T_a of 35°C there was no significant inhibition of metabolism by TET. In the control groups, metabolic rate was significantly higher at a T_a of 20°C compared with 30 ($p < 0.0012$) and 35°C ($p < 0.0002$). There was no significant difference in metabolic rate of control animals exposed to T_a's of 30 and 35°C.

Body (colonic) temperature at a T_a of 20°C decreased an average of 6.1 and 11.2°C at TET doses of 6 and 8 mg/kg, respectively ($p < 0.0001$) (Fig. 3B). At 30°C TET induced relatively small drops in body temperature, while at 35°C there was no change in temperature. While EWL did not show a significant T_a–dose interaction, there was a significant overall dose effect ($F(2,31) = 5.69$, $p < 0.0078$). This significant effect was due largely to the inhibition by TET at a dose level of 8 mg/kg at a T_a of 20°C ($p < 0.0019$) (Fig. 3C).

In the temperature gradient, control mice selected a T_a of 28 to 29.5°C (Fig. 4). ANOVA indicated that TET significantly altered this preferred temperature ($F(4,40) = 3.26$, $p < 0.021$). There was no apparent difference in thermoregulatory behavior between the 0- and 2-mg/kg treatment groups. Doses of 4, 6,

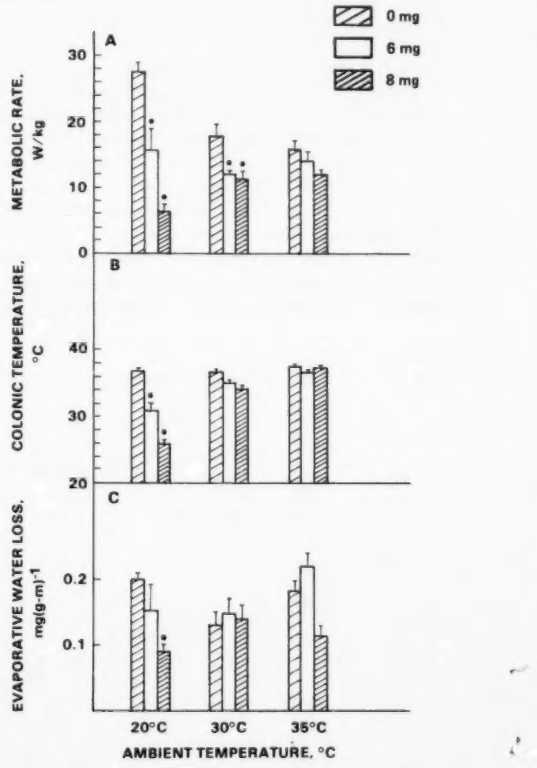

FIG. 3. Interaction of T_a and dose of TET on metabolic rate (A), colonic temperature (B), and evaporative water loss (C). $N = 4$ to 5 for each treatment group. Vertical bars represent one standard error from the mean. *Different from control, $p < 0.008$.

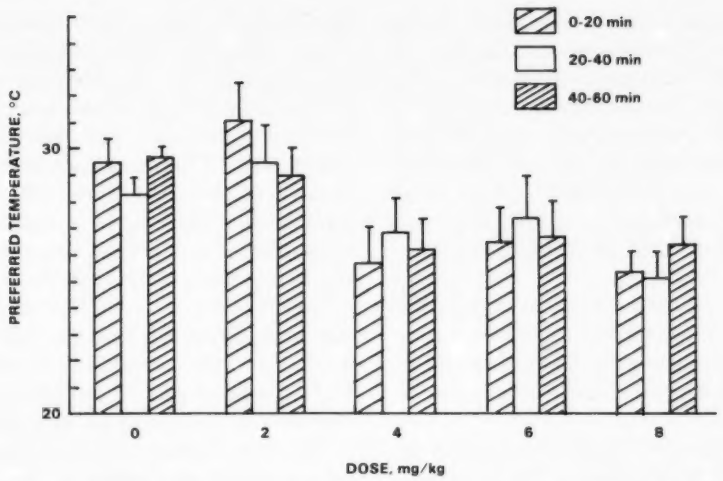

FIG. 4. Effect of TET on the preferred T_a of mice during 0 to 20, 20 to 40, and 40 to 60 min post-TET injection. $N = 9$ for each treatment group. Vertical bars represent one standard error from mean.

and 8 mg/kg all caused a reduction in preferred T_a, and at 8 mg/kg the preferred T_a was 25.2 to 26.5°C. The analysis of preferred T_a data was split into three 20-min slots with the notion that there might be a change in behavioral temperature selection with time. However, ANOVAs for time ($F(2,80) = 0.42$, $p > 0.65$) and dose · time ($F(8,80) = 1.15$, $p > 0.34$) both failed to reach significance. TET-treated animals were notably sluggish in the temperature gradient compared to controls; however, most of the animals exhibited movement to and from the warmest and coolest areas of the temperature gradient.

DISCUSSION

Intraperitoneal injection of TET inhibited metabolic rate (heat production) and induced hypothermia at T_a's of 20 and 30°C. At a relatively high T_a of 35°C, TET had little effect on metabolism and no effect on body temperature. When mice were provided with an option to select their preferred T_a, they selected a cooler T_a at TET doses of 4, 6, and 8 mg/kg. By selecting a cooler T_a the mice were apparently maintaining their body temperature at a hypothermic level. Although body temperature was not measured during the behavioral thermoregulatory experiments, it was observed earlier that TET at 6 and 8 mg/kg caused significant hypothermia at T_a's of 20 and 30°C (Fig. 3B). The observation that the mice selected a T_a of approximately 25°C when given TET at 6 and 8 mg/kg suggests that their core temperature was below normal.

Since high doses of TET resulted in depressed locomotor activity, one might question if the behavioral experiments were biased by introducing the animals on the cold side of the temperature gradient. However, when the TET-injected animals entered the temperature gradient they usually moved from the cold to the warm end repeatedly before settling down in the cool side of the gradient.

There is little direct evidence on the mechanism by which TET induces hypothermia. However, results from studies not concerned specifically with thermoregulation indicate that TET may inhibit muscular thermogenesis. The release of acetylcholine in the rat phrenic

nerve–hemidiaphragm preparation during phrenic nerve stimulation is attenuated following TET treatment (Bierkamper and Valdes, 1982). The resting membrane potential of the rat soleus muscle is significantly reduced following chronic TET administration (Millington and Bierkamper, 1982). Tonus control of skeletal muscle in mice (e.g., shivering) is critical to the normal mechanisms of heat production (Hart, 1971). This reaction may explain why, at low ambient temperatures where mice must shiver to maintain an elevated heat production, TET was most effective in inhibiting metabolic rate and inducing hypothermia.

Is the reduction in body temperature following TET administration forced or regulated? Distinctions between forced and regulated temperature changes were discussed earlier (Introduction). In the present study TET either directly or indirectly inhibited metabolic rate which apparently led to the reduction in body temperature. If the TET-induced reduction in temperature were forced, one would expect the mice to select a very warm T_a. The observation that the animals selected a cold T_a in the temperature gradient suggests a volitional reduction or regulated-like decrease in body temperature. Yehuda and Wurtman (1974) found that rats given *d*-amphetamine and placed in a cold environment avoided a heat lamp and allowed body temperature to decrease. Rats given *d*-amphetamine and placed in a warm environment remained close to a heat lamp and allowed body temperature to increase. This "paradoxical" effect of *d*-amphetamine is somewhat similar to our results except that mice given TET tended to always avoid the warm side of the temperature gradient.

At a T_a of 35°C there was no reduction in metabolic rate or body temperature. If TET induced a regulated hypothermia at this T_a, one would expect an increase in heat dissipating effectors (i.e., EWL). However, EWL was not elevated significantly at either 6 or 8 mg/kg. Mice are not well adapted to dissipate heat by EWL (Hart, 1971; Gordon, 1982). Thus, when given TET at a high T_a, a regulated hypothermia may be invoked but not accomplished because of poor autonomic heat dissipatory reflexes. The behavioral test showed that TET-treated mice avoided warm in favor of cool T_a's. Thus, following TET exposure at a high T_a, mice apparently can employ behavioral but not autonomic mechanisms to reduce body temperature.

In view of the effects of TET on behavioral thermoregulation, it is apparent that the neural control of body temperature is affected by TET. The effect of TET on temperature regulation may be due to an alteration in the levels and/or binding of neurotransmitters in the central nervous system. A lethal dose (10 mg/kg, ip) of TET to the rat causes significant decreases in brain levels of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) (Robinson, 1969). Cook (1983) found decreases in NE and dopamine in the rat brain within 30 min after TET administration (6 or 9 mg/kg, ip). On the other hand, Mailman *et al.* (1983) found little change in the levels of γ-aminobutyric acid or acetylcholine of various brain sites in rats treated daily with TET (0.3 mg/kg/day) postnatally from Days 2 to 29. The concentration and turnover of NE and 5-HT in the brainstem are crucial to thermoregulatory control (Myers, 1980). Thus, the thermoregulatory effects of TET may be partially attributable to the influence of the organotin compound on neurotransmitter levels in the central nervous system.

Dyer and Howell (1982) found that the impact of TET exposure on the latency of visually evoked responses was greater with increasing T_a. That is, the animals recovered sooner from TET injection if they were allowed to remain hypothermic at a cooler T_a. If TET induces a regulated hypothermia in the rat as it does in the mouse, then maintaining the animal at a relatively warm T_a and attenuating the TET-induced hypothermia may accentuate the neurotoxic effect of TET. It is well known that changes in ambient temperature above or be-

low thermoneutral levels can magnify the toxicity of various drugs and toxic agents (Goldberg and Salama, 1969; Klauenberg and Sparber, 1983a,b). As shown in the present study, TET-induced hypothermia was associated with a lower preferred T_a. If, following TET administration, the preferred lower T_a and body temperature cannot be selected, then the same dose of TET may be more toxic, and elevated temperatures may therefore be more stressful.

In summary, ip TET administration results in hypothermia which increases in magnitude with decreasing T_a. The hypothermia is associated with the inhibitory effects of TET on metabolic heat production. However, when given the option of selecting their thermal environment, TET-treated mice select a cooler T_a and consequently, lower body temperature. The fact that TET induces regulated hypothermia may be related to the effect of T_a on the neurotoxicity of this compound.

Since TET-induced neurotoxicity is more pronounced in rats prevented from becoming hypothermic (Dyer and Howell, 1982), one might view the regulated-hypothermia response of mice treated with TET as a survival-motivated behavioral and physiological response. Presently, these observations from the present study and Dyer and Howell (1982) are coincidental. It remains to be shown conclusively if TET-induced regulated hypothermia is a true toxicity-mediated survival response.

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